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Recurrent Invasive Pulmonary Mucinous Adenocarcinoma Showing Responses to Platinum-Based Chemotherapy Regimens with Docetaxel and Bevacizumab:A Case Report

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Introduction

The primary pulmonary mucinous adenocarcinoma is a rare variety of lung cancer that accounts for 0.24% of all lung cancers [1]. Now it is defined as tumor cells with a goblet or columnar cell morphology with abundant intracytoplasmic mucin [2]. Usually, this type of mucinous neoplasm has specific imaging findings and pathological morphology. And it is often described as a kind of neoplasm is recrudescent rapidly and resistant to radiotherapy and chemotherapy. So this tumor has a remarkably poor prognosis. Recently, some researchers reported that this tumor may have a low rate of EGFR mutation and a high rate of K-ras mutation and ALK rearrangement [3-5].These characteristics of molecular pathology may change the treatment status of the tumor.

Case

A 49-years-old man with a smoking history of more than 20 years was admitted for further management to our department in March, 2011. The patient had no relevant history of lung disease, but before admission he suffered from cough and expectoration for over 3 months. The chest computed tomography (CT) scan demonstrated a tumor in the inferior right pulmonary lobethe longest length of the tumor is about 10 cm without enlargement of hilar and mediastinal lymph nodes (cT3N0M0, IIB) (Figure 1).

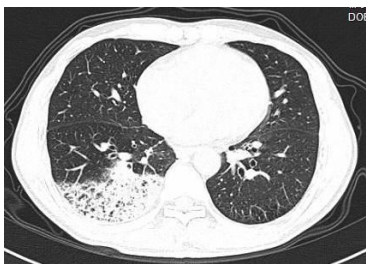

Figure 1: Computed tomography scan of lung at diagnosis. Large pulmonary consolidation and thickening of bronchial walls of posterior basal segment of inferior lobe of right lung.

CT-guided lung via-cutaneous core needle biopsy failed to confirm diagnosis of malignant disease. No other distant metastasis was found after cranial magnetic resonance imaging (MRI), abdominal CT and bone emission computed tomography (ECT) scan. An inferior right pulmonary lobectomy and mediastinal lymph nodes dissection was operated on him by thoracoscope. The pathological results confirmed the tumor was mucinous adenocarcinoma, 13 × 12 cm large in size, with no lymph node metastasis (Figure 2).

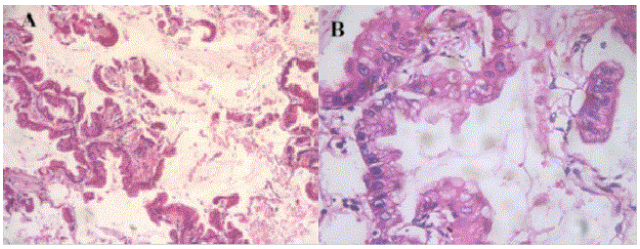

Figure 2: Hematoxylin and eosin (HE) staining of the lung tumorthe tumor was composed of abundant mucin pools that distended the alveoli. (A: 10X; B: 40X).

Mutation analysis of the EGFR gene was negative in exon 18,19,20,21. EML4-ALK translocation was also negative. A missense mutation (GGT to TGT) at codon 12 of the K-ras gene resulting in an amino acid change from glycine to cysteine was detected (Figure 3).

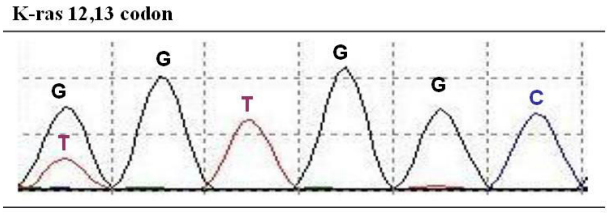

Figure 3: Mutation analysis of the K-ras gene. A missense mutation (GGT to TGT) at codon 12 of the K-ras gene resulting in an amino acid change from glycine to cysteine was detected.

The patient received 4 cycles of post–operative adjuvant chemotherapy with paclitaxel and carboplatin in the following three months. Five months after surgery, the patient suffered from cough and expectoration again. Multiple metastases were detected in the left

lung and pleura, with enlargement of right hilar lymph nodes by chest CT-scan. The patient tried several therapeutic regimens such as gemcitabine/cisplatin, pemetrexed/cisplatin, and gefitinib. But none of these regimens was effective. The tumor kept progression (Figure 4A) and the symptoms kept deteriorated. At this moment, the patient still had a good performance score and had a strong desire to try new regimens. Docetaxel/cisplatin together with bevacizumab were given as his fourth-line treatment. After 2 cycles, the symptoms of cough and expectoration were obviously improved. The CT-scan showed tumor shrinking, and efficacy assessment was partial remission (Figure 4B). Though the progression-free survival (PFS) lasted only about 5 months, it was the most effective therapeutic regimen for him in the whole case history. Grade IV myelosuppression with febrile neutropenia was happened. After progression, the best supportive care was given. The patient died in April, 2014. The overall survival is about 37 months.

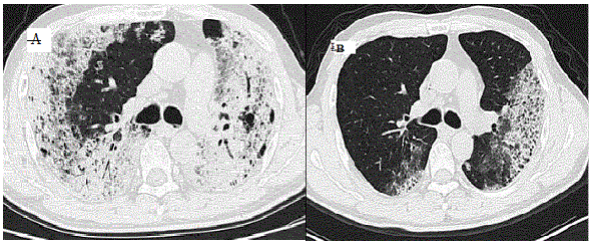

Figure 4: Computed tomography scan of lung before (A) and after(B) docetaxel /cisplatin together with bevacizumab treatment.

Discussion

This case is consistent with the common imaging and pathologic manifestation of a typical invasive mucinous adenocarcinoma. Invasive mucinous adenocarcinoma has imaging characteristic as a range of nodules to lobar replacement by a spectrum of patterns including ground—glass opacity (GGO), mixed GGO/solid foci, or consolidation [6]. Intraalveolar mucus may make the CT appearance solid or nearly solid [7]. The mucoid component may appear as homogeneous consolidation with soft-tissue attenuation that is lower than that of muscle [7]. Tumor cells with a goblet or columnar cell morphology with abundant intracytoplasmic mucin are the typical pathological features of this tumor. For this kind of the tumor, pre-operative core needle biopsy always failed to have a confirmed diagnosis. However, some literatures also suggested that these pathologic characteristics of lung invasive mucinous adenocarcinoma are similar in those from sites such as the pancreas and ovary. So clinicians should exclude primary tumors in these locations to make sure it is primary pulmonary mucinous adenocarcinoma [2,7]. Our case had typical manifestations in imaging and pathology. The diagnosis of the patient failed in a small biopsy but confirmed after surgery. Abdominal CT scan exclude the possibility of other primary malignancy in this case.

EGFR mutation is a common molecular event in non-small cell lung cancer (NSCLC). Compared to nonmucinous adenocarcinomas, mucinous adenocarcinoma had a much lower rate of EGFR gene mutation. But the mutation rate of K-ras gene was higher than those nonmucinous tumor [2]. A recent Japanese study analyzed the mutation of the EGFR gene and the K-ras gene in 45 patients with pulmonary mucinous adenocarcinoma. The result showed that the EGFR mutation rate is 7%, and the K-ras mutation rate is high to 77%. And all mutations of the K-ras gene were focused at the codon 12 [5]. EML4-ALK translocations is a relative recent event for NSCLC. Patients especially with features as solid-predominant adenocarcinomas harboring K-ras gene mutations, a cribriform morphology, and with signet-ring cell features had more probability for EML4-ALK translocations [2]. In a recent Chinese study, EML4-ALK translocations were demonstrated to be more common in patients with a solid signet-ring cell pattern and mucinous cribriform pattern [4]. The literatures also showed that EML4-ALK translocations rate of non-smokers is higher than smokers [3,4]. In this case, the patients had a K-ras missense mutation (GGT to TGT) located at codon 12, leading to an amino acid change from glycine to cystenine. The EGFR gene was wild type, and the EML4-ALK translocation was not detected.

Now it is a consensus that pulmonary mucinous adenocarcinoma may prompt poor prognosis [2,5,7]. Surgery is the best treatment choice. But patients always recur in a short time [9]. Until now, there is no standard regimen for these patients. Only few case reports reported that pemetrexed might be a good choice [10,11], and chemotherapy combined with the anti-angiogenesis agent bevacizumab may improve the response [11]. The efficacy of target therapies depends on drug-sensitive mutations [7,12]. In this case, the patient recurred soon after surgery, and kept progression during the treatment of gemcitabine/cisplatin, pemetrexed/cisplatin, and gefitinib. The poor efficacy might closely relate with his molecular background, wild type EGFR gene, no translocation of the EML4-ALK gene and a missense mutation at codon 12 of the K-ras gene. The regimen composed of Docetaxel/cisplatin and bevacizumab was his fourth-line treatment, with an efficacy of partial regression and a PFS of 5 months. This regimen containing bevacizumab was the most effective one for him during the whole history, which is consistent to the Japanese case [11]. Anyway, we cannot make a conclusion only based on several case reports, prospective randomized clinical trials are necessary. The underlying reason was still unclear, might relate with the mechanism of bevacizumab which did not work directly to the tumor but changed the microenvironment of the tumor. And although KRAS mutations were identified in patients with NSCLC more than 20 years ago, their clinical role as predictive and prognostic biomarkers remains controversial [7].

In summary, we report a case of invasive pulmonary mucinous adenocarcinoma with typical pathological features and imaging findings. The molecular analysis showed wild type EGFR gene, no translocation of the EML4-ALK gene and a missense mutation at codon 12 of the K-ras gene. The patient recurred soon after surgery, and kept progression during various treatments, including standard platinum-based chemotherapy and gefitinib. The regimen composed of docetaxel/cisplatin and bevacizumab was his fourth-line treatment, with an efficacy of partial regression and a PFS of 5 months. This regimen containing bevacizumab was the most effective one for him during the whole history. Further prospective randomized clinical trials are necessary.

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